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REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 41 and 54-56 are pending in the application and presented for examination. Claim 41 is currently amended. Claims 55 and 56 are newly added. Claim 54 was withdrawn by the Examiner as being drawn to a non-elected invention. Reconsideration is respectfully requested.

Claim 54 was withdrawn by the Examiner as being drawn to a non-elected invention. Applicants respectfully traverse this restriction requirement. Claim 54 names a specific compound that falls within the scope of the elected inventive group. Applicants respectfully request that claim 54 be rejoined and examined on its merits.

I. FORMALITIES

Support for new claim 55 is found, for example, in claim 41 as originally filed. Moreover, support for the cholic acid chemical structure is found, *inter alia*, in Example 12. In Example 12, the name of the final product "3'-N-gluconamidopropyl-3"-N-cholamidopropyl-N-cholamide" clearly indicates that the cholic acid group has been incorporated in to Formula I as an "N-cholamido" and an "N-cholamide" group. One skilled in the art would readily recognize that "N-cholamido" or "N-cholamide" means that the cholic acid is connected to Formula I as part of an *amide* group. Support for new claim 56 is found, *inter alia*, in Example 12 as filed. More specifically, the chemical group shown in claim 56 is a glucono-lactone fragment, which is the saccharide reagent that is used in Example 12 (*see*, page 31, line 4).

As such, no new matter is present in this or any other portion of the present amendment.

II. FIRST REJECTION UNDER 35 U.S.C § 112, FIRST PARAGRAPH

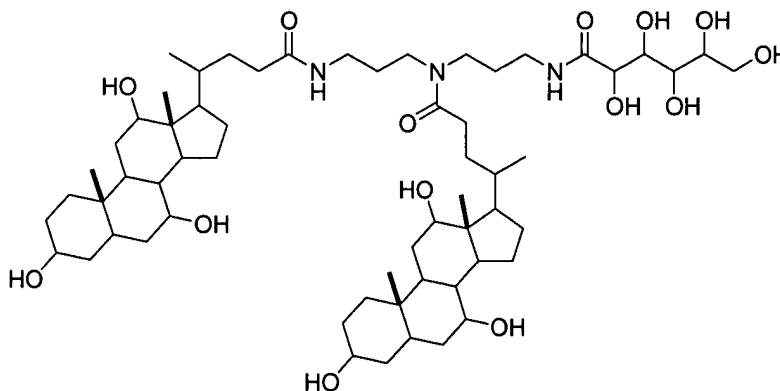
Claim 41 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the Applicants, at the time the application was

filed, had possession of the claimed invention. In response, Applicants respectfully traverse the rejection.

The Examiner alleges that neither is the structure of Impurity II disclosed in the application, nor is its structure readily apparent from the application as filed because of the broad scope of possibilities described for the X_1 , X_2 and X_3 groups. Presently amended claim 41 and newly added claim 55 are focused on novel compounds having Formula I, wherein X_1 and X_2 are both cholic acid groups, X_3 is a pentose or hexose monosaccharide group, and three carbons link the nitrogen atoms in the core of Formula I (n is 3). The subject matter embodied in claims 41 and 55 is supported by the original application as filed. The specification teaches that a preferred compound of the present invention contains cholic acid groups at both X_1 and X_2 , a saccharide group at X_3 , and three carbons linking the nitrogen atoms in the core of Formula I (*see*, page 5, lines 2-10). X_3 is clearly defined as a pentose or hexose monosaccharide group (*see*, page 4, lines 31-32). In addition, original claim 48, distinctly sets forth a preferred embodiment of the invention in which X_1 and X_2 are both cholic acid groups and X_3 is a monosaccharide, in particular a hexose monosaccharide. Moreover, Example 12 specifically teaches how to make a compound of Formula I (*see*, page 31, lines 15-19).

A skilled artisan would readily recognize that the compound prepared in Example 12, to be a compound of Formula I as claimed wherein X_1 and X_2 are cholic acid groups and X_3 is a monosaccharide having the structure shown below (*see below*, Figure 1). The identity of the compound from Example 12, as depicted below in Figure 1, is unambiguously supported by the mass spectral data presented on page 31, lines 25-27 showing a mass to charge ratio peak (m/z) of 1090.6 which corresponds to product molecular weight of $MW=1089.7$ g/mol.

Figure 1: Product from Example 12, Molecular Weight 1089.74 g/mol

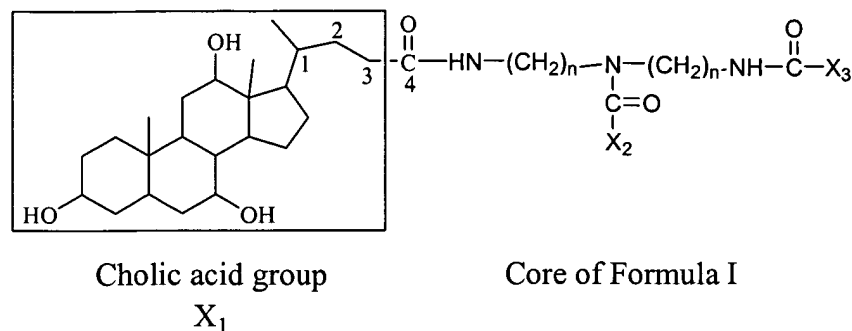


Thus, Applicants assert that a compound of Formula I as set forth in claims 41 and 55 is clearly and adequately described in the specification and supported by way of an Example.

In addition, the Examiner alleges that the specification, as originally filed, does not disclose the manner in which cholic acid is attached to the compound of Formula I. Applicants respectfully disagree with the Examiner.

Referring to Example 12 of the instant application, Applicants assert that one skilled in the art would immediately recognize that during the synthesis of a compound of Formula I, the reaction of the cholic acid (a carboxylic acid) starting material is first reacted with isobutylchloroformate (an acid chloride derivative) to form a mixed anhydride intermediate followed by subsequent reaction with 3-aminopropyl-3'-N-glucoamidopropyl-amine (an amine), will result in a formation of an amide bond in which the carbonyl group of the amide group in the core of Formula I will have originated from the cholic acid starting material.

Figure 2:



Applicants submit that the chemical reactions used to attach the cholic acid group to the core of Formula I are common synthetic transformations well known to one skilled in the art as shown by the fact that an analogous set of transformations is described in the introductory organic textbook titled "Introduction to Organic Chemistry¹." The following reactions are described therein: 1) the reaction of an acid chloride derivative and a carboxylic acid to form an anhydride; and 2) the reaction of an anhydride with an amine (*see*, Appendix). Relevant sections from the Appendix are reproduced in Figures 3 and 4 (below) for the Examiner's convenience.

Figure 3: Reaction and an acid chloride with a carboxylic acid.

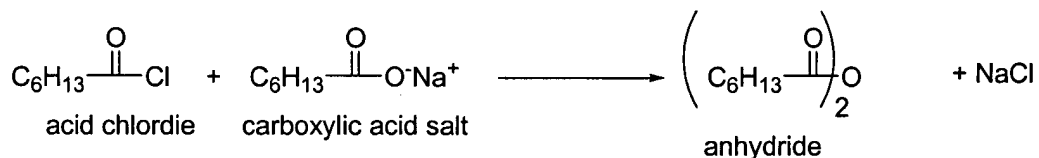
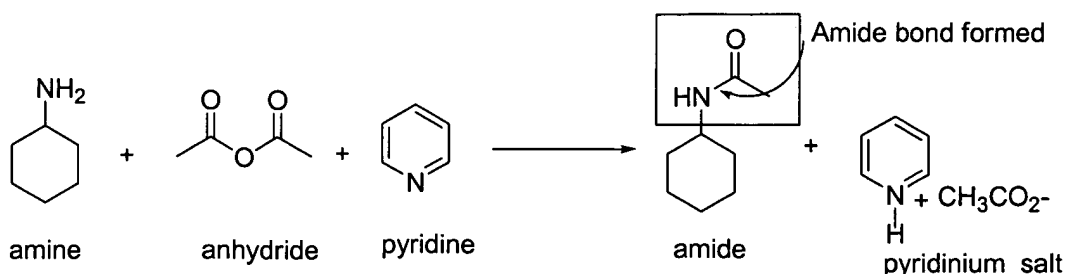


Figure 4: Reaction of an anhydride with an amine.



¹ Introduction to Organic Chemistry, 4th Ed.; 1992; Prentice-Hall, Inc., pgs. 530-531.

As such, Applicants submit that the specification does teach and disclose how a cholic acid group is attached to a compound of Formula I. Therefore, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph rejection.

In view of the foregoing, it is evident that the subject matter now being claimed, was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claim 54 simply uses IUPAC nomenclature to name and claim a compound within the elected inventive group. As such, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph rejection.

III. SECOND REJECTION UNDER 35 U.S.C § 112, FIRST PARAGRAPH

Claim 41 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. In response, Applicants respectfully traverse the rejection.

The Examiner alleges that the structure of Impurity II is not readily apparent from the specification as originally filed because the specific combination of X₁, X₂ or X₃ could not have been guessed and thus it would have required one of skill undue experimentation to determine how to make or use the compounds claimed as Impurity II. Claims 41 and 55 now set forth embodiments of Formula I wherein the X₁ and X₂ groups are both cholic acid groups and the X₃ is a pentose or a hexose monosaccharide. Applicants assert that a compound having the structure of Formula I is clearly and adequately described in the specification (*see*, page 4, lines 31-32; page 5, lines 2-10; page 31, lines 15-19 and 25-27). Moreover, the specific disclosure of an embodiment of Formula I in which X₁ and X₂ are cholic acid groups and X₃ is a monosaccharide, such as a hexose monosaccharide is found in claim 48 as filed. As such, Applicants submit that the particular embodiments of the invention, as set forth in claims 41 and

55, are clearly and sufficiently disclosed and claimed in a manner consistent with 35 U.S.C. § 112. Further, claim 54 uses IUPAC nomenclature to name and claim a specific compound having Formula I of the instant application. Therefore, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph rejection.

The Examiner also alleges that the manner in which cholic acid is attached at X₁ and X₂ of Formula I is not disclosed in the specification. Applicants respectfully disagree with the Examiner for the reasons previously set forth in Section I of the present amendment. Again, the specification provides a clear example of how a compound of Formula I is prepared (*see*, Example 12). The reactions used in the synthesis described in Example 12 are well known in the art as evidenced, in part, by the fact that these reactions are taught in an *introductory* organic chemistry textbook. As such, Applicants submit that a skilled artisan, following the synthesis described in Example 12, would undoubtedly recognize how the cholic acid group is attached to a compound of Formula I. As such, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph rejection.

IV. REJECTION UNDER 35 U.S.C § 112, SECOND PARAGRAPH

The Examiner rejected claim 41 under 35 U.S.C. § 112, second paragraph, as being indefinite as allegedly the claim is unclear with regard to how the cholic acid group is attached to Formula I. In view of the amendment to the claims, Applicants respectfully traverse the rejection.

The Examiner alleges that the addition of cholic acid to Formula I may result in 1) building 4 carbon atoms between the carboxyl group and the pentose ring of cholic acid; 2) removal of the carboxyl group of cholic acid; or 3) attachment of cholic acid to Formula I *via* one of the hydroxyl groups. The Examiner alleges that it is unclear whether Applicants intend the claim to encompass any means of attaching cholic acid to Formula I at X₁ and X₂ or if the claim is limited to the removal of the carboxyl group on cholic acid. In view of the amendment to the claim, Applicants respectfully traverse the rejection.

Applicants have amended claims 41 and 55 to clearly set forth the manner in which the cholic acid group is attached in Formula I. The connectivity of the cholic acid groups to Formula I as shown in the amended claims is supported by Example 12 which describes the synthesis of 3'-N-gluconamidopropyl-3"-N-cholamidopropyl-N-cholamide, a compound of the present invention. Applicants assert that the connectivity of the cholic acid groups is readily apparent from the name of the final product. Specifically, the name of the final product "3'-N-gluconamidopropyl-3"-N-cholamidopropyl-N-cholamide" clearly indicates that the cholic acid group has been incorporated in an "*N-cholamido*" and in an "*N-cholamide*" group. One skilled in the art would readily recognize that "*N-cholamido*" or "*N-cholamide*" means that the cholic acid has been incorporated into Formula I as part of an amide group. Of the three scenarios presented by the Examiner for attaching a cholic acid group to Formula I, the only option that would result in the integration of the cholic acid group into Formula I as a "N-cholamido" group as is presently taught and claimed is option 2, which gives the appearance that the carboxylic acid group of cholic acid being removed.

In view of the amendment to the claims, Applicants submit that the claim *is* clear with regard to how the cholic acid group is attached to Formula I. As such, Applicants respectfully request the rejection under 35 U.S.C. § 112, 2nd paragraph be withdrawn.

V. CONCLUSION

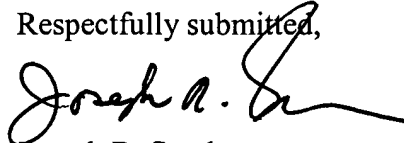
In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

Appl. No. 08/889,355
Amdt. dated July 9, 2004
Amendment under 37 CFR 1.116 Expedited Procedure
Examining Group

PATENT

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

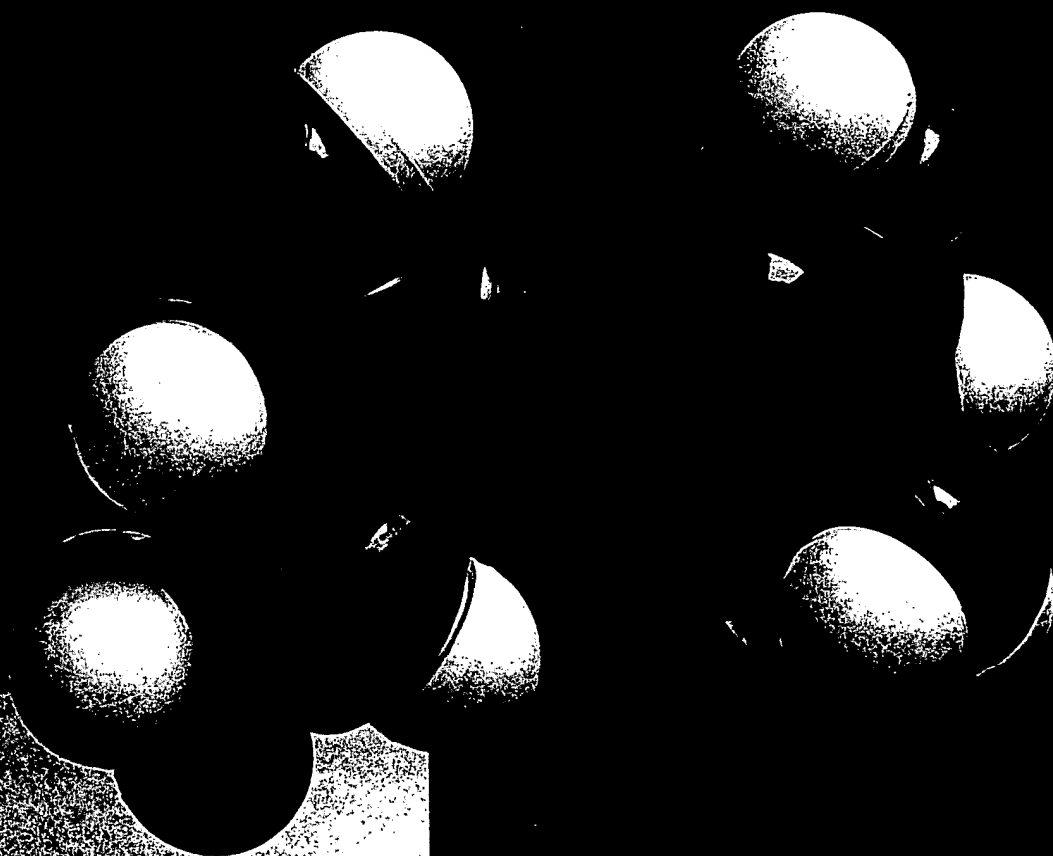
A handwritten signature in black ink, appearing to read "Joseph R. Snyder", with a stylized flourish at the end.

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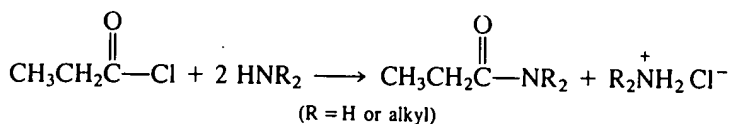
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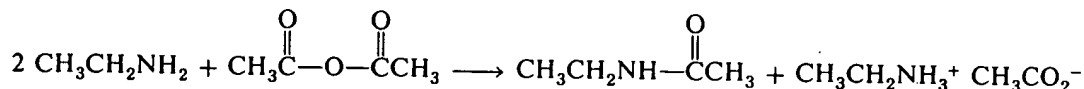
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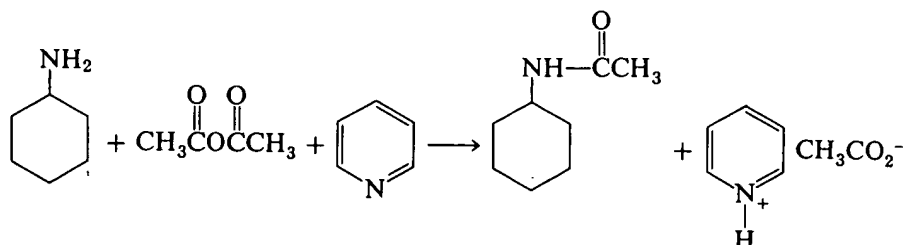


The reaction of ammonia and amines with anhydrides follows a similar course; the products are 1 mole of amide and 1 mole of carboxylic acid. Since the liberated acid reacts to form a salt with the ammonia or the amine, it is necessary to employ an excess of that reactant.

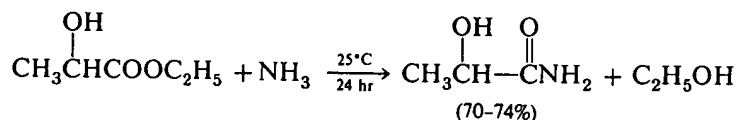


As in the analogous reaction of amines with acyl halides, one may carry out the reaction in the presence of one equivalent of tertiary amine.

Figure 4
of Response



Esters also react with ammonia and amines to yield the corresponding amide and the alcohol of the ester. This synthetic path is useful in cases where the corresponding acyl halide or anhydride is unstable or not easily available. An interesting example of such a case is

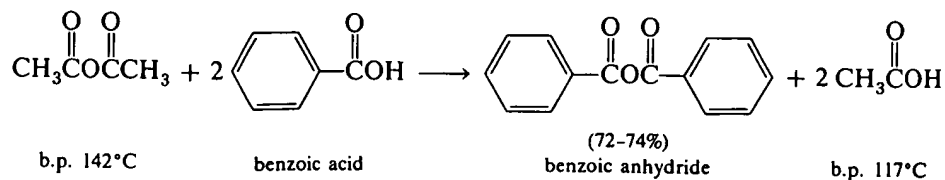


In this case the acyl halide method for preparing the amide may not be used, since the molecule contains an OH group, which will react rapidly with an acyl halide.

EXERCISE 19.7 Treatment of 2-hydroxypropanoic acid (lactic acid) with thionyl chloride gives a product having the formula C₆H₈O₄. Propose a structure for this material.

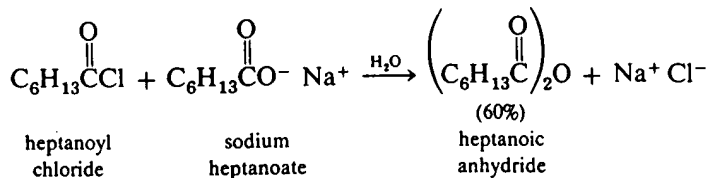
C. Reaction of Acyl Halides and Anhydrides with Carboxylic Acids and Carboxylate Salts. Synthesis of Anhydrides

The reaction is preparatively useful when the anhydride is acetic anhydride. In this case, acetic acid can be removed by distillation as it is formed because it is the most volatile component in the equilibrium mixture.



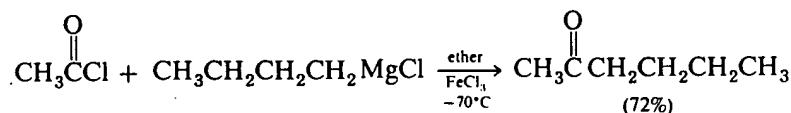
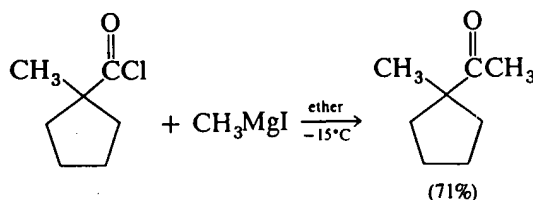
The only carboxylic acid derivatives that undergo a useful reaction with carboxylate salts are acyl halides. The product is an anhydride.

Figure 3
of Response

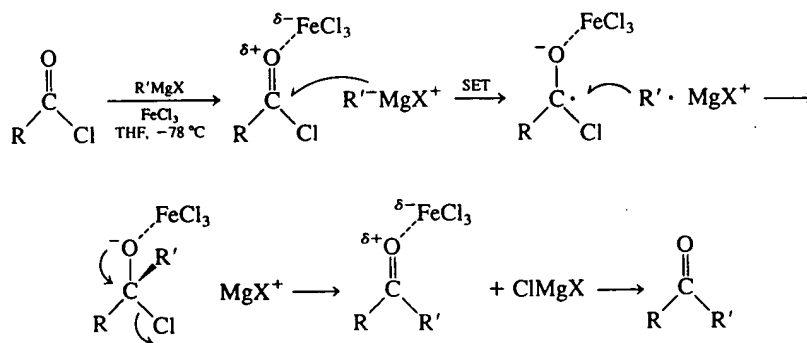


D. Reaction with Organometallic Compounds

Acyl halides react with various organometallic reagents to give ketones. Since ketones are



Ferric chloride may serve as a Lewis acid, complexing with the oxygen of the acyl chloride. Many organometallic reactions are now thought to proceed by **single electron transfer (SET)**. The carbanion of the Grignard transfers an electron to the acyl chloride–ferric chloride complex to yield a stabilized radical anion and a highly reactive alkyl radical. The radical then combines with the radical anion to form the “tetrahedral intermediate” familiar from our discussion of hydrolysis. The intermediate decomposes to yield the ketone, magnesium halide and the catalyst ferric chloride.



(See Sections 8.6 and 8.8.) Rapid reaction at low temperatures is consistent with an SET mechanism.

If excess Grignard reagent is used the product ketone reacts further, giving a tertiary alcohol.